REMARKS

Reconsideration is requested.

Claims 17-20, 22-30 and 32-38 are pending. The Examiner is requested to appreciate that claims 21 was canceled in the Amendment filed November 28, 2008. Claims 40 and 41 have been added. Support for the amendments may be found throughout the specification, such as at page 6, lines 9 and 10. No new matter has been added. Claims 17-20, 22-30, 32-38, 40 and 41 will be pending upon entry of the present Amendment. Entry of the present Amendment is requested to advance prosecution.

The Section 112, second paragraph, rejection of claim 29 is obviated by the above amendments. Entry of the present Amendment will, at a minimum, reduce this issue for appeal. Entry of the present Amendment and withdrawal of the rejection are requested.

To the extent not obviated by the above amendments, the Section 103 rejection of claims 17-20, 22-30 and 32-38 over Omori (DNA Repair 2002, pp 299-310) in view of Marthinet (Gene Therapy 2000, Vol. 7, pp 1224-1233) and Klem (U.S. Patent Application Publication No. 2003/0176376), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

Omori et al suggest that inhibition of Ku70 could be applied therapeutically by using an antisense oligonucleotide targeted to Ku70 suppressing Ku70 protein expression.[1]

Martinet et al and Klem et al disclosed a transcriptional decoy strategy using double-stranded oligodeoxynucleotides targeting a specific transcriptional factor in order to decrease the expression of a protein.

On the basis of these teachings, the applicants submit, with due respect, that one of ordinary skill in the art would not have been were "well aware" of the design principle of "decoys" in general, as alleged by the Examiner[2] . Martinet et al and Klem et al teach how to design a transcriptional decoy, but not any decoy.

Therefore, the teachings of Martinet et al and Klem et al could only suggest, at best, the design of a decoy targeting a transcription factor involved in the expression of Ku70 protein and that transcriptional decoy could be an equivalent of the antisense oligonucleotides used by Omori et al.

Even if one of ordinary sill in the art would have been motivated to prepare a transcriptional decoy of Ku70, the presence of specific transcriptional elements to be targeted is not known. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation of success in using a transcriptional decoy targeting Ku70 protein.

However, it cannot be said, based on Martinet et al and Klem et al, that one of ordinary skill in the art would not have recognized that a decoy oligomer directly

[1] See first sentence of page 4 of the Office Action dated March 3, 2009.

targeting Ku protein is an equivalent agent to an antisense oligonucleotide. The teachings of Martinet et al and Klem et al only concern transcriptional factor and there is nothing in the cited art which would have allowed one of ordinary skill in the art to have reasonably predicted that this mechanism can be generalized to any kind of proteins.

The cell presents a complex environment and there is no teaching or suggestion in the cited art that a decoy able to be bound by a protein is able to have a blocking effect on it. The Examiner's generalization in this regard is unjustified.

The double stranded decoy molecules inhibit the NHJE pathway, and not only Ku70 as suggested by Omori et al. As summarized in the Background section of the present application, many approaches have been conceived to inhibit individually the key proteins involved in the NHJE pathway. It has been noted by the inventors that these approaches share a common unfavourable feature in that they target a **single** effecter with possible bypass. In particular, these strategies may be thwarted by mutations in the target or over activation of an alternative repair pathway.

The decoy molecules of the invention are not an equivalent agent to an antisense oligonucleotide targeting Ku70. The antisense oligonucleotide suppresses the Ku70 protein expression, thereby only inhibits Ku70. The decoy molecules of the invention do not block the effect of Ku70 but use the Ku70 effect to inhibit the NHJE pathway. Accordingly, the presence of Ku70 is necessary to reach this effect. In addition, the decoy molecules of the invention use the capacity of Ku70 to recruit other proteins factors to inhibit the NHJE pathway.

[2] See last paragraph, page 4 of the Office Action dated March 3, 2009.

The decoy molecules of the invention are substrates for proteins involved in the NHEJ pathway, including Ku protein but not limited to this protein. The binding of Ku protein is the first step of the strategy. However, the binding of Ku on the decoy molecule is not sufficient to reach the sensitizing effect of the decoy molecules. The decoy molecules must also be able to activate H2AX phosphorylation. Phosphorylated H2AX acts as a tag of DSB on chromosomes and allows the increase of local concentration of repair factors near the lesion.

In short, and without limitation, the applicants submit that the decoy molecules of the invention are recognized as DSB by the signalling and repair proteins hijacking them away from the chromosome DSB to be repaired, thereby increasing the sensitivity of the cells to DNA damaging therapy as the "real" DSBs on chromosome are not repaired on time. The decoy molecules of the invention act through the induction of "false" DNA damage signalling and impair DNA repair of damaged chromosomes. The fact that the decoy molecules of the invention target a cascade of complexes involved in DSB repair activity, instead of a unique protein, reduces the possibility of developing resistance during treatment.

This is why the design of the decoy molecules was not straight forward or a predictable invention for one of ordinary skill in the art. One of ordinary skill in the art could have possibly designed a molecule in order to be just bound by Ku protein and fail to reach the sensitizing activity. The basis of the mechanism is more complex than the blocking of the protein's binding site.

Example 2 (Figures 1) of the present application shows that, except the 8-bp DRIL8-PEG molecule, the DRIL molecules (16, 24 and 32bp) are able to be bound by Ku70 protein. However, only the DRIL molecules of at least 24 bp are able to significantly increase the sensitivity of cells (Example 3.1 and Figure 2.1; Example 4 and Figures 3.1-3.4).

The decoy molecules disorganize damage signalling and DNA repair by mimicking DSBs and recruiting the proteins involved in DSB signalling and repair. As shown in example 4, the DNA repair foci have been detected through H2AX phosphorylation detection. The DRIL-32 molecules trigger similar cell response as if DNA damages were occurred in nuclei (Figure 3.2), whereas the molecule of 16 bp is too short. In addition, the DNA damage signalling has also been detected through p53 phosphorylation and p53 was found to be highly phosphorylated with DRIL-32 molecules whereas DRIL-16 molecule only induces moderate phosphorylation (Figure 3.3).

In conclusion, the decoy molecules of the invention are not inhibitory agents of Ku70 but use it to recruit other proteins factors to inhibit the NHJE pathway. Accordingly, Omori et al teach away from the invention because they suggest to inhibit Ku70 protein. The teachings of Martinet et al and Klem et al are not so broad to concern the design principle of any decoy molecule. In addition, while one of ordinary skill in the art could possibly design a molecule in order to be just bound by Ku protein, it would not have been obvious from the cited art to have made the sensitizing activity because Ku is necessary but not sufficient. The decoy molecules of the invention do not block the

effect of Ku70 but use the Ku70 effect to inhibit the NHJE pathway by jamming DBS damage signalling. This effect is length-dependent as demonstrated in the present application.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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